CNS Neuroscience & Therapeutics

REVIEW

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Negative Symptoms in Schizophrenia: Where We have been and Where We are Heading

Jean-Michel Azorin, Raoul Belzeaux & Marc Adida

Department of Psychiatry, Sainte Marguerite Hospital, Marseille, France

Keywords
History; Negative symptoms; Pathophysiology; Psychopathology; Schizophrenia; Treatment.

Correspondence
J.-M. Azorin, Department of Psychiatry, Sainte Marguerite Hospital, 270 Bd Sainte Marguerite, 13274 Marseille, Cedex 9, France.
Tel.:+33491744082;
Fax: +33491745578;
E-mail: jazorin@ap-hm.fr
Received 24 January 2014; revision 6 May 2014; accepted 6 May 2014

SUMMARY

This review traces the history of negative symptom profiles in neuropsychiatry from their earliest emergence in the 19th century to the current psychiatric concepts and therapeutic approaches. Recent investigations performing exploratory and confirmatory factor analysis have suggested that negative symptoms are multidimensional, including evidence for at least two distinct negative symptom subdomains: diminished expression and amotivation. Preliminary studies have demonstrated the clinical validity of this distinction. Several potential pathophysiological validating factors based on brain imaging analysis of emotional experiences and expressions in individuals with schizophrenia are examined. Finally, the potential of different treatment strategies, including medications and various psychotherapeutic techniques, to most favorably treat each of these subdomains is discussed.

doi: 10.1111/cns.12292

Introduction

Although negative symptoms have long been recognized as an integral and clinically meaningful component of schizophrenia, this concept has evolved over time, and targeted symptomatic treatment has remained largely unsatisfactory.

To encourage the development of treatments in this area, the National Institute of Mental Health organised a Consensus Development Conference on Negative Symptoms in 2005. The consensus statement issued from this conference noted that the domains of negative symptoms may involve distinct neurobiological substrates and may represent separate therapeutic targets. This consensus statement also encouraged a clearer definition of the negative symptom subdomains and the development of new assessment tools. In line with this approach, regulatory agencies, such as the Food and Drug Administration, encouraged the development and potential approval of adjunctive therapies proven to be specifically effective for negative symptoms [1].

The aim of the current article is to summarize some of the recent advances in the pathophysiological understanding and treatment of negative symptoms and to align these advances with the more traditional understanding of these symptoms based on a historical perspective. A key focus is the deconstruction of negative symptoms into distinct subdomains, as well as the likely impact of this distinction on the elucidation of these symptoms.

Historical Aspects

The history of the negative/positive dichotomy of schizophrenia symptoms has already been addressed in several reports [2–5]. In this review, we would like to insist on the different meanings it may actually cover and the influence that this diversity is likely to exert on our understanding of schizophrenia. The evolution and characterization of the negative symptoms of schizophrenia are summarized in Table 1.

The distinction between negative and positive symptoms was first introduced by Reynolds [6] in the context of epilepsy. Negative symptoms were conceived as the negation of vital properties, resulting in loss of sensation, paralysis, and coma; positive symptoms referred to an excess of vital properties, such as clonic jerking, abnormal movements, and even hallucinations and delusions.

This distinction was elaborated further by Jackson [7] in keeping with Herbert Spencer's ideas regarding the dissolution and evolution of the nervous system. Jackson hypothesized that negative symptoms are related to the dissolution of neural function, whereas positive symptoms resulted from excitation or the release of lower level inputs from higher inhibitory control.

As indicated by Messinger et al. [5], Reynolds considered positive and negative symptoms as distinct manifestations of the same pathology, whereas, according to Jackson, pathology produced a loss of higher inhibitory control, which primarily manifested as

Table 1 Negative symptoms of schizophrenia: evolution of concepts and characteristics

Early concepts of negative symptoms in neuropsychiatry
Loss of vital properties, Ref. [6]
Loss of higher neural functions, Ref. [7]
Loss of intrapsychic structure, Ref. [13]
Decrease in CNS arousal levels, Ref. [10]
Early descriptions of negative symptoms in schizophrenia
Defect in emotional experience driving poor motivation, absence of pleasure, and lack of interest, Ref. [8]
Disconnection between cognition and emotion, resulting in apparent indifference despite intact emotional experience, Ref. [9]
Modern concepts of negative symptoms in schizophrenia
Symptoms that characterize schizophrenia associated with neuronal loss, Ref. [14]
Primary negative symptoms, as manifestations of core pathology versus secondary negative symptoms, as consequences of the illness, Ref. [15]
Current psychometric approaches addressing the negative symptoms of schizophrenia
Affective flattening, alogia, anhedonia, asociality, and avolition (amotivation) as most common individual items included in rating scales
Expressive deficits (flat affect, alogia) and avolition (amotivation, anhedonia, asociality) as most common groupings in factor analysis studies

negative symptoms, and subsequent manifestations of the disinhibited lower level processes indirectly induced positive symptoms.

However, in the opinion of both Reynolds and Jackson, the symptoms observed were not directly caused by the lesion of the nervous system [3].

Although not referring to these concepts, Kraepelin [8] was the first to provide a thorough description of what we currently define as negative symptoms. Kraepelin emphasized that "we meet everywhere the same fundamental disorders in the different forms of dementia praecox ... in very varied conjunctions, even though the clinical picture may appear at first sight ever so divergent".

According to Kraepelin, these fundamental disorders included cognitive deficits, such as attention deficit or mental poverty, and a core deficit in emotional experience [4]. The latter causes the absence of feelings that is responsible for "dulled appearance" (blunted affect), as well as the absence of pleasure (anhedonia) from activities, the absence of a "desire for activity", poor motivation and a "complete loss of volitional impulse". This results in an indifference to the external world and a lack of interest in one's surroundings, which reinforces mental poverty; patients are also indifferent to themselves, including their physical health, which results in decreased pain sensation and poor hygiene [5]. Kraepelin [8] also described a "loss of inner unity of the activities of intellect, emotion and volition in themselves and among one another", but he did not impute any hierarchical relevance to this disorder or to other symptom subdomains.

In contrast, Bleuler [9] considered this loss of inner unity as a manifestation of the primary psychopathological process of the disease, that is, a loosening of the associations that are generated at all psychological levels. He contrasted the "primary symptoms" that are directly produced by the disease process with the "secondary" symptoms that are "partly psychic functions operating under altered conditions, and partly the results of more or less successful attempts at adaptation to the primary disturbances". Bleuler [9] considered the disturbance in emotional experience which produces apparent indifference as a secondary symptom, believing that affectivity therefore remained intact as a mental function: "Thus there can be no doubt at all that the psyche's capacity to produce affects has not disappeared in schizophrenia".

This less pessimistic view gave rise to an overemphasis on positive manifestations in the middle of the past century, which was marked by the predominant interest devoted to the so-called first rank symptoms [5].

Nevertheless, it was also at that time that Snezhnevsky [10] first applied the positive versus negative distinction to schizophrenia symptoms. This distinction emerged from the "Pavlovian" understanding that the level of arousal is the predominant factor in nervous system activity. In this context, positive and negative schizophrenic symptoms are modeled as two ends of a bell curve representing the level of arousal in humans, in which negative symptoms are exhibited by individuals experiencing exceedingly low arousal levels, and positive symptoms are exhibited by individuals whose arousal levels are exceedingly high. Even if this model did not become very popular, the distinction that the model was based on did. This approach resulted in a new series of empirical studies on positive and negative symptoms, with some authors, such as Wing and Brown [11], including social withdrawal among negative symptoms, while others, such as Strauss et al. [12], categorizing it into a third entity. In France, in a theoretical manner, Ey [13] hypothesized that negative symptoms reflected a loss of intrapsychic structure secondary to organic processes, whereas positive symptoms constitute recovery mechanisms by healthy brain areas.

However, in the 1980s, Crow [14] provided the presently used distinction between positive and negative symptoms. He proposed that schizophrenia could be separated into two distinct subtypes based on the relative prevalence of positive and negative symptoms. Type 1, or positive syndrome schizophrenia, is characterized by positive symptoms that are caused by a disturbance in dopaminergic system activity. Type 2, or negative syndrome schizophrenia, is hypothesized to be characterized by negative symptoms that are caused by an underlying mechanism stemming from neuronal loss; therefore, Type 2 schizophrenia may belong to the field of neuroanatomy rather than neurochemistry. Type 2 schizophrenia has also been considered to be marked by a predominance of cognitive deficits.

A further development of this model was the distinction between primary and secondary negative symptoms by Carpenter et al. [15]. The former were hypothesized as enduring and result-

ing in a "deficit syndrome" indicative of a fronto-temporo-parietal dysfunction against a background of global impairment. Therefore, primary negative symptoms may be manifestations of core pathology. In contrast, secondary negative symptoms may be considered as mere consequences of other illness symptoms or their treatment, such as symptoms of depression, coping strategies for paranoid symptoms or side effects of antipsychotic medications.

Historically, it is notable that the most recent models of negative symptoms tend to accentuate an "ontological" difference within this subgroup, which was not the case for the first descriptions of these symptoms. In fact, it is postulated that if symptoms are "truly" negative, they are the more or less a direct expression of a nervous system lesion and are therefore generally not amenable to treatment. This hypothesis is in contrast with Bleuler's understanding, as well as that of Henri Ey, or even Jackson and Reynolds, who considered these symptoms as secondary to an underlying pathology.

Psychopathological Aspects

The development of psychometry has facilitated considerable progress in the understanding of negative symptoms and their respective role in the psychopathology of schizophrenia. The likely most well-known of the rating scales of negative symptoms is the Scale for the Assessment of Negative Symptoms (SANS) [16]. The SANS consists of five subscales: (1) affective flattening or blunting, (2) alogia, (3) avolition-apathy, (4) anhedonia-asociality, and (5) attentional impairment. Blunted affect contains three components: decrease in facial expressions; decrease in expressive gestures and other body language; and decrease in the modulation of the volume, pitch, and speed of speaking [17]. Alogia is a decrease in verbal output or verbal expressiveness, often referred to as poverty of speech. Avolition or amotivation includes both a subjective reduction in interests, desires and goals and a behavioral reduction in self-initiated and purposeful acts. Anhedonia is the inability to experience pleasure from positive stimuli, and asociality is the lack of involvement in social relationships of various types. Finally, attentional impairment refers to social inattentiveness as well as inattentiveness to mental status examination. Recent factor analyzes, however, have consistently demonstrated that attentional impairment is more closely related to cognitive dysfunction than negative symptoms [18]. For the most part, factor analysis studies examining the structure of negative symptoms have reported the existence of two separate factors, "expressive deficits" and "avolition", providing evidence that the deficits in emotional expression and volition are two distinct symptom domains in schizophrenia that encompass all of the variability in negative symptoms [5,18]. In those studies, "anhedonia/asociality" was highly correlated to "avolition/apathy", whereas alogia contributed to the "expressive deficit" factor [5,18]. This two-factor characterization was also found for rating scales of negative symptoms aside from the SANS; interestingly, this two-factor structure emerged even when using the Schedule for the Deficit Syndrome (SDS) scale, which is designed to assess the so-called primary negative symptoms or deficit syndrome [19].

In keeping with these findings, the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus panel has proposed that a two-factor model may best account for negative symptoms: blunted affect-poverty of speech and anhedonia–asociality–avolition [20]. The validity of these subgroups has been recently confirmed by a study demonstrating that distinct subgroups of patients exhibiting increased avolition-apathy (AA) or diminished expressiveness (DE) could be identified within schizophrenia and finding clinically meaningful differences in presentation [21]. Compared with the DE group, the AA group was: (1) more likely to have a family member who had been hospitalized for psychiatric reasons, (2) less likely to be gainfully employed, (3) less likely to complete high-quality work, (4) more likely to experience poorer premorbid social adjustment, (5) more likely to experience a gradual onset of psychosis, and (6) more likely to be male. Compared with the AA group, the DE group displayed a greater likelihood of: (1) being African-American, (2) experiencing an abrupt onset of psychosis, and (3) undergo a longer duration of hospitalization.

As patients exhibit varying degrees of symptoms of both the AA and DE dimensions, clinical interest remains in the understanding of the contribution of each type of symptomatology to ultimately appropriately tailor the therapeutic approach to the symptomatology of each patient. Research should focus on the underlying pathology of each dimension and its associated neurocircuitry to inform treatment decisions.

The emphasis placed on these dimensions has fostered the development of new rating scales that include an adequate sampling of AA and DE symptoms, such as the Brief Negative Symptom Scale (BNSS) [22] and the Clinical Assessment Interview for Negative Symptoms (CAINS) [23].

The DSM-5 [24] has taken into account these findings by stating that "two negative symptoms are particularly prominent in schizophrenia: diminished emotional expression and avolition". Highlighted by the initial inclusion and posterior exclusion of attentional impairment, the relationship between negative and cognitive symptoms has been the focus of growing interest. This interest is in line with the investigation as to whether negative symptoms may occur as a direct consequence of a structurally based deficit, as has been postulated in some of the reports described above. Correlations were found between negative symptoms and various measures of neuropsychological performance in cross-sectional studies. However, longitudinal studies have failed to establish a relationship between changes in negative symptoms and neurocognitive function. Negative symptoms appear to account for only a small proportion of the variance in cognitive impairment. Therefore, most authors agree that although negative symptoms and cognitive impairment often occur together, negative symptoms do not directly cause cognitive impairment or vice versa, and as a result, they do not change in parallel over time [18].

The complexity of the relationship between cognitive impairment and negative symptoms has been further illustrated by several studies that shed light on the aforementioned controversy between the (neo) Kraepelinian and Bleulerian conceptions regarding the putative deficit in emotion among schizophrenia patients. For example, Kring et al. [25] measured the startle response magnitude both during viewing and after removal of emotional pictures to determine whether individuals with and without schizophrenia differed in their patterns of immediate

responses to emotional pictures and of the maintenance of these responses. It was found that individuals with and without schizophrenia did not differ in their self-reported or startle response magnitude during the presentation of emotional pictures. However, healthy controls maintained these responses after the stimuli were removed from view, while individuals with schizophrenia did not. It was concluded that individuals with schizophrenia do not exhibit a deficit in consummatory pleasure (consummatory anhedonia) but instead exhibit a deficit in anticipatory pleasure (anticipatory anhedonia). In the same vein, Heerey and Gold [26] used an experimental paradigm that measured self-reported ratings of pleasure and the degree of effort exerted to seek or avoid exposure to images of varying valences in the present and the future. The schizophrenia patients were found to exhibit deficits in their ability to couple their behavior to the motivational properties of a stimulus, despite equivalent subjective in-the-moment pleasure ratings for these stimuli, compared with healthy controls. Moreover, significant correlations were detected between these deficits and working memory impairment, particularly for situations requiring the maintenance of internal representation of the stimulus. It was concluded that schizophrenia patients may exhibit a diminished capacity to anticipate that the pursuit or achievement of a goal will be pleasurable, which results in an impairment in the translation of subjective experiences into actions. These studies demonstrate the mechanism by which cognitive deficits may alter emotion and motivation in schizophrenia patients and elucidate the nature and the specificity of their apparent deficits. Conversely, other studies have demonstrated the impact that these motivation deficits may exert on cognitive dysfunction. When examining the role of effort in cognitive functioning in schizophrenia, Gorissen et al. [27] found that insufficient effort, in line with motivational deficit, accounted for up to one-third of the variance in neuropsychological test performance.

These studies examining the relationships between cognitive function and negative symptoms also contribute to the validation of the autonomy of the anhedonia–asociality–avolition factor and shed light on its role in the psychopathology of this disease.

Pathophysiological Aspects

It would be interesting to search for neurobiological markers of these distinct negative symptom dimensions, which would both corroborate their validity and facilitate the pathophysiological understanding of schizophrenia.

Based on a facial emotion identification task performed during high-field magnetic resonance imaging, Gur et al. [28] found that schizophrenia patients displayed reduced limbic system activation compared with controls during the emotion identification task. However, whereas in controls, increased amygdala activation was associated with correct identification of threat-related (anger and fear) expressions, schizophrenia patients exhibited the opposite effect, in which increased limbic activation led to misidentifications. Interestingly, increased amygdala activation in response to the presentation of fearful faces was strongly correlated to an increased severity of flat affect. This result was interpreted as reflecting a lack of habituation of amygdala activation due to repeated presentations of fearful faces, which may also involve the hippocampus [29]. As demonstrated by Rosenkranz et al. [30], the prefrontal cortex (PFC) may regulate aspects of affective behavior, such as learning and emotional expression, by interacting with the lateral nucleus of the amygdala (LAT). Furthermore, the regulation of LAT neuronal plasticity may reflect a role of the PFC in the formation of associations. Loss of frontal regulation, such as that observed in schizophrenia, not only results in inadequate attenuation of the response to an affective stimulus, but may also lead to more pervasive problems associated with an inability to regulate amygdala plasticity. Therefore, potential outcomes may include the formation of abnormal associations and the inability to maintain extinction behaviors that have been learned to offset inappropriate associations. The correlation between affective flatness and increased amygdala responses to fearful faces suggests that the former may be an adaptive response to prevent the formation of abnormal associations and/or a surrogate for extinction behaviors. In support of this hypothesis, Stip et al. [31] found that schizophrenia patients exhibiting blunted affect when presented with film excerpts depicting sad and neutral social situations displayed both hypofrontality and dysfunctional circuitry that was distributed throughout the brain compared with patients lacking blunted affect. They hypothesized that the temporal and midbrain activation detected in the flat affect group could indicate that these brain regions were more active to compensate for inactivation in other regions. The midbrain, for instance, has been found to evoke passive emotional coping strategies (that is, quiescence, immobility, and hyporeactivity) characterized by disengagement or withdrawal from the external environment and sympatho-inhibition. In general, this coping might subsequently result in reduced activity of the cortical regions necessary for the correct identification of facial expressions [28].

In keeping with these findings, Fakra et al. [32] used an intuitive emotional task (matching emotional faces) to examine the neural basis and dynamics of facial affect processing in schizophrenia patients compared with healthy controls. The patients failed to activate the regions of the limbic system implicated in the automatic processing of emotion. Furthermore, the patients exhibited decreased activation of the regions involved in holistic face processing and increased activation of the regions associated with feature analysis. The authors concluded that the distribution of neocortical network activity observed during the intuitive task indicated that schizophrenia patients may resort to feature-based, rather than configuration-based, processing and that this network may constitute a strategy to compensate for limbic system dysfunction. In a re-analysis of their data [33], they found that the schizophrenia patients exhibited similar amygdala activation to the controls during the initial stage of processing, but that the level of amygdala activation decreased during the sustained stage. It is attractive to speculate that this failure in the automatic and habitual processing of emotions is associated with the loss of natural self-evidence, which, according to some authors [34], may account for the social withdrawal as well as the slowness and inactivity that are characteristic of the negative syndrome. With respect to anhedonia, Juckel et al. [35] compared unmedicated patients with healthy controls using an incentive monetary delay task, in which visual cues predicted that a rapid response to a subsequent target stimulus would result in either a monetary gain or loss or no consequence. This task was also presented during functional magnetic resonance imaging. In healthy controls,

reward anticipation was associated with activation of regions that included the nucleus accumbens and several other limbic and prefrontal areas, whereas the schizophrenia patients failed to activate this network during the reward anticipation phase. This difference was interpreted as contributing to symptoms such as anhedonia, apathy and loss of drive and motivation. Crespo-Facorro et al. [36] explored the pattern of brain responses to olfactory stimuli in schizophrenia patients and healthy controls via positron emission tomography. They found that the patients experienced unpleasant odors in a manner similar to healthy controls, but the patients exhibited impairment in the experience of pleasant odors. Analysis of the regional cerebral blood flow revealed that the patients failed to activate limbic/paralimbic regions (e.g., the insula, the nucleus accumbens, and the parahippocampal gyrus) during the experience of unpleasant odors, instead recruiting a compensatory set of frontal cortical regions. They concluded that rather than using the frontal cortex to recognize a pleasant stimulus as pleasurable, the prefrontal cortex was overactivated in response to an unpleasant stimulus.

Recent neuroimaging studies have also emphasized the role of the default-mode network in the pathophysiology of negative symptoms [37–39]. The default-mode network consists of a network of brain regions that displays increased activity when individuals are allowed to feel undisturbed. The default-mode network comprises regions including the ventromedial prefrontal cortex, the precuneus, the posterior cingulate cortex (PCC), the retrosplenial cortex, the inferior parietal lobule, the lateral temporal cortex, the dorsomedial prefrontal cortex, and the hippocampal formation. It has been associated with autobiographical memory, mental simulation, theory of mind, and self-referential processing. Using a voxel-based morphometric technique, Lee et al. [37] found that regional gray matter (GM) volumes in the left precuneus and the right PCC of schizophrenia patients showed trend level negative correlations with trait anhedonia scores. As the default-mode network is involved in self-referential processing, decreased GM volume in the precuneus and PCC could be related to decreased self-awareness of emotion (alexithymia), which may explain anhedonia. The relationship found in several studies between alexithymia and anhedonia is likely to give support to this hypothesis [37]. Because the default-mode network has also been associated with envisioning the future, the authors hypothesized that upon exposure to a cue indicating future pleasure, an individual with schizophrenia would not anticipate this pleasure, which would result in anticipatory anhedonia. Interestingly, this study also detected a correlation between the GM volume in the precentral gyrus in the patient group and trait anhedonia. The precentral gyrus forms the core of the classic motor mirror neuron system (MNS), which is involved in the observation and imitation of others' actions. Therefore, this finding suggests increased activity of the MNS in patients exhibiting trait anhedonia, which could indicate that anhedonic schizophrenia patients may tend to rely on the classic motor MNS more than the theory of mind (ToM) network to comprehend others due to the dysfunction of the ToM network. This hypothesis is in accordance with recent studies revealing that ToM function did not originate from the classic motor MNS, but rather from a distinct network that may correspond to the default-mode network [40]. This result is in agreement with the clinical observations that patients exhibiting predominant negative symptoms often present with symptoms such as echopraxia, echolalia or echomimia, which have been combined under the rubric of "mannerism" [13].

Therapeutic Considerations

Studies examining the effect of treatments on the negative symptom subgroups are rare, which is likely primarily because the vast majority of studies have used the Positive and Negative Syndrome Scale (PANSS) to measure negative symptoms.

A clinical drug trial evaluated the effect of mirtazapine in schizophrenia outpatients with persistent negative symptoms despite at least 1 year of clozapine therapy [41]. The clozapine doses were not modified throughout the duration of the study (8 weeks). Patients with other psychiatric comorbidities or a history of substance abuse were excluded. The primary outcome measure of this study was not specified. At baseline, no significant differences between the two groups in the SANS and Brief Psychiatric Rating Scale (BPRS) scores were detected. Significant differences in the SANS total score were detected at week 4 ($P < 0.05$) and week 8 ($P < 0.01$) between the mirtazapine group and the placebo group. Statistically significant improvements in two SANS subscales, avolition-apathy and anhedonia-asociality, were detected with mirtazapine treatment compared with placebo treatment; however, no significant differences were detected in the scores on the alogia, affective flattening, or attention components of the SANS. The value of a study such as this is to demonstrate that drugs may have a selective effect on specific subdomains of negative symptoms, in this case the AA subdomain.

In another study, add-on therapy with 5 mg/day of selegiline, a selective monoamine oxidase inhibitor, was evaluated in a 12-week placebo-controlled trial in 67 schizophrenia patients with persistent negative symptoms [42]. The subjects were maintained on a stable antipsychotic dose. Their baseline severity of negative symptoms was assessed using the SANS. They exhibited no prominent positive symptoms based on the BPRS thinking disturbance items, and no patients were diagnosed with a mood disorder at the time of the study. Changes significantly favouring selegiline over placebo were evident in the SANS total and avolition-apathy and anhedonia global scores, the BPRS total score, and the Clinical Global Impression severity and improvement scores. There were no significant group differences in the positive, depressive, or extrapyramidal symptoms. This study confirms a specific effect of the drug on the AA subdomain of negative symptoms, which appears to be independent of any effect on other types of symptoms.

On the other hand, in a 12-week, double-blind placebo-controlled trial of 86 stable schizophrenic patients treated with antipsychotics, galantamine (an acetylcholinesterase inhibitor and a positive allosteric modulator of nicotinic receptors) was found to improve alogia only, suggesting a specific effect of this drug on the DE subdomain [43]. Atypical antipsychotics, such as clozapine, were also found to improve DE symptoms based on the BPRS withdrawal-retardation subscale [44]. However, contrary to the results observed for galantamine, in this study, significant changes in the global negative symptom scores were also detected.

A systematic review on the effects of the combination of antipsychotic and antidepressant drug treatment for the management of negative symptoms in schizophrenia reported that more individuals receiving combination therapy exhibited clinically significant improvement in negative symptoms than those receiving an antipsychotic and a placebo. Significant differences were detected in various aspects of negative symptoms: "affective flattening", "alogia", and "avolition". Nevertheless, the authors concluded that the amount of information was currently too limited to allow for any firm conclusions [45].

Regardless, it is possible that some drugs, such as amisulpride [46], which was found to improve all the five SANS component subscores, are efficient on both the DE and AA subdomains. Preliminary evidence indicates that this could be also the case for a partial alpha-7 nicotinic receptor agonist, 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A), when administered as adjunctive treatment [47].

With respect to psychotherapies and psychosocial treatments, there is increasing evidence of their potential efficacy for negative symptoms of schizophrenia [48–50]. Arts therapies are complex interventions that combine psychotherapeutic techniques with activities aimed at promoting creative expression. They comprise art psychotherapy, dance movement therapy, body psychotherapy, drama therapy, and music therapy. All of these interventions focus on the creation of a therapeutic working relationship in which strong emotions can be expressed and processed, emphasizing expression, communication, social connection and self-awareness through supportive and interactive experiences. In all arts therapies, the creative process is used to facilitate self-expression within a specific therapeutic framework and to enable the patient to experience him/herself differently and develop new ways of relating to others [49]. A meta-analysis conducted on six randomized-controlled trials (RCTs) containing any type of control revealed that arts therapies were consistently effective in reducing negative symptoms compared with any control. Moreover, preliminary evidence suggests the efficacy of arts therapies on both the DE [51,52] and AA [51–53] subdomains.

Social skills training (SST) approaches have been developed to address impairments in social skills. Skills training programs involve a common set of strategies for teaching new skills based on social learning theory, including goal setting, role modeling, behavioral rehearsal, positive reinforcement, corrective feedback, and homework assignments, to help promote generalization to the community. A meta-analysis of 22 RCTs, which included 1521 patients, found that SST approaches displayed a moderate average effect size on improving negative symptoms and a moderate average effect size on improving social adjustment and independent living [54]. An effect of SST approaches on the AA subdomain of negative symptoms was found in some studies [55].

Cognitive remediation programs have been designed to address the problem of cognitive impairment in schizophrenia. They employ a variety of methods, such as drill and practice exercises, teaching strategies to improve cognitive impairments, and group discussions. A meta-analysis of cognitive remediation programs for schizophrenia found only a small effect size on negative symptoms, which could be expected due to the relative independence of cognitive function and negative symptoms [56]. However, two studies [57,58] have demonstrated an improvement in the DE subdomain following cognitive remediation. More sophisticated techniques targeting the cognitive control of emotion and focusing on the anticipatory pleasure and motivation deficits in schizophrenia also appear to be promising [59].

Finally, there is growing evidence based on RCTs and meta-analyses that cognitive behavioral therapy (CBT) may be beneficial in reducing the severity of negative symptoms [50]. According to phenomenological accounts of patients participating in CBT, it has been proposed that specific cognitive appraisals and beliefs may play a role in the expression and persistence of negative symptoms [60]. Among the former, Rector et al. [60] have highlighted the role of low expectancies for pleasure, low expectancies for success, low expectancies due to stigma and perception of limited resources. Specific negative expectancy appraisals are likely to be associated with each of the negative symptom domains. These phenomenological data appear to be in line with the findings from experimental studies on deficits in anticipatory pleasure [25]. Negative symptoms are considered to represent, in part, a compensatory pattern of disengagement in response to anticipated failure in tasks and social activities. A psychological aspect of this motivational and behavioral inertia appears to be the patient's perception of limited psychological resources-a perception that motivates patients to conserve energy by minimizing investment in activities requiring effort [60]. The major interest of this model is to provide differentiated hypotheses likely to account for the determinism of various negative symptoms. Support for this model would be garnered if treatment studies were to demonstrate that reductions in negative symptom subgroups are associated with corresponding (and correlating) reductions in specific pessimistic expectancy appraisals [60]. In fact, some studies have indicated that CBT could be efficient on both the DE [61,62] and AA [63,64] subdomains of negative symptoms.

Future Directions

There are still several critical issues that remain to be addressed to improve the current understanding and treatment of negative symptoms. A first conceptual issue involves the nature and assessment of the DE and AA factors. Although these factors are likely to reflect distinct underlying processes associated with schizophrenia, it cannot be excluded that these factors may reflect a measurement artifact unrelated to these biological processes [65]. As indicated by Blanchard and Cohen [65], DE items may cohere because they are related to the behavioral observation of interpersonal expression during an interview, whereas AA items may aggregate because they are observed during social activity outside an interview based on a patient's self-report. To minimize this measurement bias, it is of utmost importance to use negative symptom assessment tools that systematically measure experiences and behaviors corresponding to each of the targeted subdomains [66]. Progress has recently been made in this area [22,23].

In keeping with this progress, it may be of interest to develop assessment tools that involve the patient's family as well as family therapy programs that may provide patients with more opportunities to engage in social activities and behaviors due to the help and involvement of the family members [66].

With respect to advancing the understanding of underlying neurobiology of schizophrenia, progress is underway in adopting

a translational approach to examine the negative symptoms of schizophrenia—that is, investigations translating laboratory findings to the development of new treatments [67]. It has been recently suggested [68] that, in individuals with schizophrenia, the AA dimension may reflect difficulties in using internal representations of emotional experiences, previous rewards, and motivational goals to drive current and future behaviors in a way that would allow them to obtain desired outcomes. Based on these proposals, specific interventions have been designed to address the emotional and cognitive processes that may underlie the motivation and pleasure deficits of schizophrenia patients with prominent negative symptoms. For example, Favrod et al. [69] found that patients with severe anhedonia who benefited from a cognitive–sensory intervention aimed at increasing the anticipation of pleasure displayed improvement on the anticipatory scale of the Temporal Experience of Pleasure Scale. Daily activities of the patients were also increased.

Likewise, Johnson et al. [70] demonstrated that loving-kindness meditation helped schizophrenia patients to manage their emotions and increased their anticipatory pleasure, which was associated with a decrease in anhedonia and overall negative symptoms.

However, these studies are small, open trials that require replication with larger samples and in randomized-controlled trials [67].

Another issue which deserves further attention is the use of combined treatments, as different treatments may differ in their efficacy for DE and AA symptoms. For instance, one study that used combined psychosocial treatment (assertive community treatment, multifamily groups, psychosocial education, and SST), in patients with first episode psychosis, found a greater improvement on the DE and AA subdomains among patients receiving the combination treatment compared with those who received a standard treatment [71]. In studies like this, there is a need to assess which components of various treatments may be useful to treat DE or AA symptoms; therefore, if treatments are combined, studies should include groups randomly assigned individual treatment components to determine whether the combined treatment yields additional benefits [66].

Finally, as many pharmacological agents have been evaluated for the treatment of negative symptoms [72], it would be of great interest to systematically assess their respective efficacy on DE and AA symptoms using sensitive and validated scales. This is also of interest to understand what are the potential pharmacological bases of the efficacy toward to a specific dimension of negative symptoms.

Conclusions

Ten years ago, a model was proposed by Phillips et al. [73] describing the neural bases of the observed deficits in emotion perception and behavior in schizophrenia. According to this model, structural and functional abnormalities within the limbic system, including the amygdala, the anterior insula, and the ventral striatum, could result in a restriction of the identifiable range of emotions, a subsequent decrease in the range of affective states and behaviors, and a misinterpretation of non-threatening or ambiguous stimuli as threatening. These phenomena were postulated to be perpetuated by impairments in reasoning, contextual processing, and effortful regulation of affective states, originating from structural and functional abnormalities within the hippocampus and dorsal prefrontal cortical regions. This pattern of abnormalities was also considered to be associated with negative symptoms, including emotional flattening, anhedonia and avolition/asociality. Progress in the identification of meaningful distinct subdomains within the domain of negative symptoms, along with the improvement of psychometric tools and neuroimaging techniques, may facilitate an improved understanding of the pathophysiology of negative symptoms and help determine the validity of theories posed by the fathers of modern psychiatry and of models such as the aforementioned one. The availability of novel drug treatments and new psychotherapeutic methods should also contribute to resolving these issues.

Acknowledgments

The authors would like to thank Dr Justine Lalonde (Roche SAS, France) for her correction of the English text and Carole Berioux (Convergence) for editorial assistance, which was funded by Roche.

Conflict of Interest

Jean-Michel Azorin has received research support and has acted as a consultant and/or served on a speaker's bureau for Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Roche and Sanofi-Aventis. Raoul Belzeaux has received grant/research support from Lundbeck and Servier. Marc Adida has received grant/research support from Lilly and Servier.

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